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SYNTHESIS OF TETRAHYDRO-1,3-OXAZIN-2-ONES AND -2-THIONES FROM ESTERS OF N-(3-OXOALKYL)CARBAMIC AND -DITHIOCARBAMIC ACIDS

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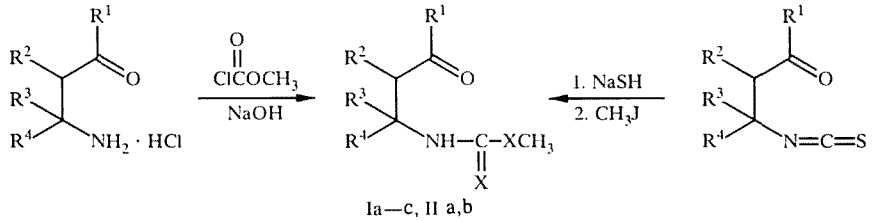
A study has been made of the interaction of N-(3-oxoalkyl)carbamates and -dithiocarbamates with sodium borohydride; it has been shown that, depending on the pH of the reaction medium, the interaction may produce either tetrahydro-1,3-oxazin-2-ones and -2-thiones, or N-(3-hydroxyalkyl)carbamates and -dithiocarbamates.

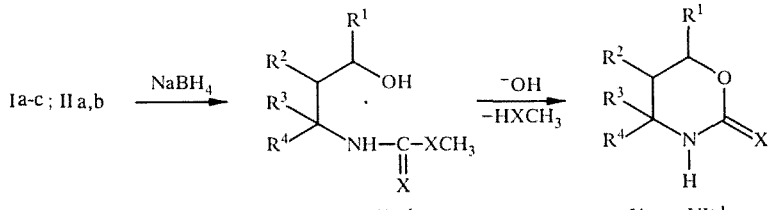
Substituted N-(3-hydroxyalkyl)carbamates and -dithiocarbamates, which are prepared from difficultly accessible 1,3-aminoalcohols, are used extensively in synthesizing derivatives of 1,3-oxazine and 1,3-thiazine [1-3]. At the same time, there are convenient methods available for the synthesis of N-(3-oxoalkyl)carbamates and -dithiocarbamates [4, 5]. In view of this situation, it appeared necessary to investigate the possibility of reducing the carbonyl group to hydroxyl in these compounds. To this end, by methoxycarboxylation of 1,3-aminoketones, we obtained methyl N-(3-oxoalkyl)carbamates (Ia-c), and by a method given in [5] we obtained dithiocarbamates (IIa,b).



Ia—c, II a,b

I X = O; II X = S; a $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$; b $R^1 = R^3 = R^4 = CH_3$, $R^2 = H$; c $R^1, R^2 = -(CH_2)_4-$, $R^3, R^4 = -(CH_2)_5-$

In our investigation of the interaction of the carbamates Ia,c and the dithiocarbamate IIa with sodium borohydride, we found that we were unable to isolate the primary reaction products, i.e., the N-(3-hydroxyalkyl)carbamates IIIa,c and the dithiocarbamate IVa, since they are unstable under the conditions of the reaction and are converted to the tetrahydro-1,3-oxazin-2-ones (Va,c) and -thione VIa, respectively. We were able to accomplish the synthesis of compounds IIIa and IVa only in a neutral medium, which we maintained by adding phosphate buffer to the reaction mixture.



III a-c; IV a,b — V a-c VI a,b

III, V X = O; IV, VI X = S

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TABLE 1. Characteristics of Compounds I-VI

Compound	Empirical formula	mp, °C (solvent) and bp, °C (P, mm Hg)	IR spectrum, ν, cm^{-1}			Yield, %
			N—C=X	CO (OH, NH)	NH	
Ia	$C_7H_{13}NO_3$	72...73 (0,4)	1710	1730	3280	68,8
Ib	$C_8H_{15}NO_3$	73...75 (0,6)*	1710	1725	3280	93,7
Ic	$C_{14}H_{23}NO_3$	91...92	1700	1715	3270	91,6
IIIa	$C_7H_{15}NO_3$	93...96 (0,3)	1695	(3130...3500)		86,0
IIIb	$C_8H_{17}NO_3$	88...90 (0,26)	1695	(3140...3480)		92,1
IVa	$C_7H_{15}NOS_2$	—	1520	(3050...3500)		75,8
IVb	$C_8H_{17}NOS_2$	—	1530	(3040...3500)		85,3
Va	$C_6H_{11}NO_2$	78...79*[2] (acetone)	1710	—	3280 3460	81,4
Vb	$C_7H_{13}NO_2$	126...126*[3] (acetone)	1710	—	3255 3440	86,9
Vc	$C_{13}H_{21}NO_2$	212...213 (acetone)	1700	—	3275 3450	93,0
VIa	$C_6H_{11}NOS$	110...112*[4] (alcohol)	1570	—	3120	92,9
VIb	$C_7H_{13}NOS$	210...211*[5] (alcohol—water)	1560	—	3165	98,7

*[1]Literature bp 70°C/0.2 mm Hg [17].

*[2]Mixture of isomers.

*[3]Literature mp 125-125.5°C (acetone) [18].

*[4]By crystallization, the trans-isomer was isolated; literature mp 111-112°C (alcohol) [11].

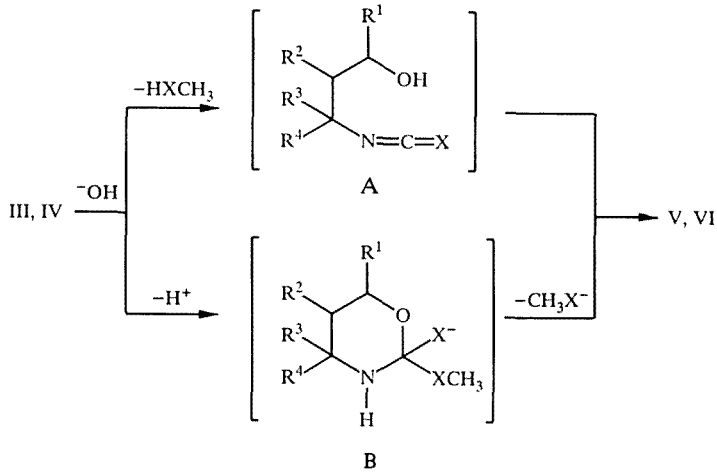
*[5]Literature mp 212-213°C (alcohol).

The reductive cyclization of the carbamates Ia,c and the dithiocarbamate IIa proceeds more readily than that of compounds Ib and IIb, which have a smaller number of substituents in the alkyl fragment. Within only a few hours after adding sodium borohydride, the carbamates Ia,c and IIa are converted almost completely to the tetrahydro-1,3-oxazines Va,c and VIa. Methyl N-(2-methyl-3-hydroxybutyl-1)carbamate IIIb and the dithiocarbamate IVb are less susceptible to cyclization in comparison with IIIa,c and IVa, so that IIIb and IVb can be obtained from Ib and IIb without using a buffer mixture. Only an increase of the pH of the reaction medium leads to conversion of the carbamates IIIa and IVa into the 1,3-oxazines Va and VIa.

As an explanation of the accelerated cyclization of polysubstituted bifunctional compounds, a concept had been proposed previously [6] on the basis of a comparison of the enthalpy and entropy for linear and cyclic structures in a series of substituted hexanes and cyclohexanes; the rates of cyclization of compounds III and IV are consistent with this concept. A similar influence of the position and number of substituents on the heterocyclization process had been noted previously in [7-9]. It can be assumed that the conversion of the hydroxycarbamates III and dithiocarbamates IV to 1,3-tetrahydrooxazines V and VI proceeds along a path that includes the formation of (respectively) isocyanato- or isothiocyanato alcohols A, the same as in the case of reductive cyclization of 1,3-isothiocyanatoketones [10-12]. Since the rate of formation of the 1,3-oxazines V and VI depends on the number of substituents in the alkyl chain of the respective linear predecessors, the limiting stage of the reaction is obviously the cyclization; therefore, we might hope to detect the intermediate 1,3-isothiocyanato alcohols A that we had obtained previously by a different method [12, 13]; in the present work, these compounds were used as reference spots. However, we were unable to register the alcohols A in the reaction mixture by means of TLC. Hence we consider that a different mechanism is more probable — one that includes a stage of formation of the intermediate B, which, being stabilized by elimination of a methoxy or mercapto anion, is converted to the tetrahydro-1,3-oxazine.

TABLE 2. ^1H NMR Spectra of Compounds I-VI

Compound	Chemical shifts, δ, ppm; and J, Hz
Ia	5,38 s (1H, NH), 3,37 s (3H, OCH_3), 3,22 dd (1H, N—CH_2, ^2J = 6,5, ^3J = 6,5), 3,15 dd (1H, N—CH_2, ^2J = 6,5, ^3J = 6,5), 2,74 m (1H, CH, ^3J = 6,5, ^3J = 6,5, ^3J = 6,5), 2,10 s (3H, $COCH_3$), 1,08 d (3H, CH_3, J = 6,5)
Ib	5,18 s (1H, NH), 3,48 s (3H, OCH_3), 2,76 s (2H, CH_2), 2,03 s (3H, $COCH_3$), 1,29 s (6H, $2CH_3$)
Ic	4,97 s (1H, NH), 3,58 s (3H, OCH_3), 3,03 dd (1, CH, ^3J = 5,0, ^3J = 13,0), 2,12...1,10 m (18H, $9CH_2$)
IIIa erythro	5,62 s (1H, NH), 3,79 m (1H, CH—O, ^3J = 6,5, 3J = 3,0), 3,58 s (3H, OCH_3), 3,50...2,87 m (2H, N—CH_2), 1,68...1,35 m (1H, CH), 1,05 d (3H, CH_3, ^3J = 6,5), 0,76 d (3H, CH_3, ^3J = 7,0)
IIIa threo	5,62 s (1H, NH), 3,58 s (3H, OCH_3), 3,50...2,87 m (3H, CH—O, N—CH_2), 1,68...1,35 m (1H, CH), 1,10 d (3H, CH_3, ^3J = 6,5), 0,80 d (3H, CH_3, ^3J = 7,0)
IIIb	6,48 s (1H, NH), 3,97 m (1H, CH—O), 3,83 s (1H, OH), 3,43 s (3H, O—CH_3), 1,63 dd (1H, CH_2, ^2J = 14,5, ^3J = 9,0), 1,33 dd (1H, CH_2, ^2J = 14,5, ^3J = 2,5), 1,28 s (3H, CH_3), 1,25 s (3H, CH_3), 1,05 d (3H, CH_3, ^3J = 6,0)
IVb	8,90 s (1H, NH), 4,18 m (1H, CH—O, ^3J = 9,5, ^3J = 6,5, ^3J = 2,0), 2,56 s (1H, OH), 2,49 s (3H, S—CH_3), 1,92 dd (1H, CH_2, ^3J = 9,5, ^2J = 15,0), 1,69 s (3H, CH_3), 1,65 s (3H, CH_3), 1,59 dd, (1H, CH_2, ^3J = 2,0, ^2J = 15,0), 1,25 d (3H, CH_3, ^3J = 6,5)
Va trans	6,80 s (1H, NH), 4,00 m (1H, CH—O, ^3J = 10,0, ^3J = 6,5), 3,45...2,85 m (2H, N—CH_2), 1,76 m (1H, CH), 1,32 d (3H, CH_3, ^3J = 6,5), 0,92 d (3H, CH_3, ^3J = 6,5)
Va cis	6,74 s (1H, NH), 4,42 m (1H, CH—O, ^3J = 6,5, ^3J = 3,5), 3,45...2,85 m (2H, N—CH_2), 2,06 m (1H, CH), 1,26 d (3H, CH_3), ^3J = 6,5), 0,97 d (3H, CH_3, ^3J = 6,5)
Vb	7,31 s (1H, NH), 4,38 m (1H, CH—O, ^3J = 3,5, ^3J = 7,0, ^3J = 12,0), 1,50 dd (1H, CH_2, ^3J = 3,5, ^2J = 12,0), 1,38 dd (1H, CH_2, ^2J = 12,0, ^3J = 12,0), 1,26 d (3H, CH_3, ^3J = 7,0), 1,23 s (6H, $2CH_3$)
Vc trans	6,23 s (1H, NH), 3,98 m (1H, CH—O), 2,33...0,90 m (19H, CH, $9CH_2$)
Vc cis	6,23 s (1H, NH), 4,55 m (1H, CH—O), 2,33...0,90 m (19H, CH, $9CH_2$)
VIa-trans	8,99 s (1H, NH), 4,15 m (1H, CH—O, ^3J = 9,6, ^3J = 6,3), 3,38 m (1H, N—CH_2, ^2J = 12,8, ^3J = 5,2, ^3J = 5,0), 2,96 m (1H, N—CH_2, ^2J = 12,8, ^3J = 10,5), 1,91 m (1H, CH), 1,41 d (3H, CH_3, ^3J = 6,3), 1,04 d (3H, CH_3, ^3J = 7,0)
VIa cis	8,91 s (1H, NH), 4,57 m (1H, CH—O), ^3J = 6,6, ^3J = 3,0), 3,46 m (1H, N—CH_2, ^2J = 12,8, ^3J = 5,2, ^3J = 1,9), 3,12 m (1H, N—CH_2, ^2J = 12,8, ^3J = 5,2, ^3J = 3,2), 2,21 m (1H, CH), 1,38 d (3H, CH_3, ^3J = 6,6), 1,02 d (3H, CH_3, ^3J = 6,6)
VIb	8,61 s (1H, NH), 4,47 m (1H, CH—O, ^3J = 11,4, ^3J = 6,0, ^3J = 2,5), 1,85 m (1H, CH_2, ^2J = 13,4, ^3J = 2,5, ^4J = 1,5), 1,63 dd (1H, CH, ^2J = 13,4, ^3J = 11,4), 1,44 d (3H, CH_3, ^3J = 6,0), 1,36 s (3H, CH_3) 1,33 s (3H, CH_3)



The structures of the compounds I-VI that were obtained have been confirmed by the results of elemental analysis, IR spectroscopy, and ^1H and ^{13}C NMR spectrometry (see Tables 1-3).

In the IR spectra of the carbamates III and the dithiocarbamates IV, recorded in a thin layer of the substance, there is no carbonyl-group absorption band in the 1725-1730 cm^{-1} region — a band that is characteristic for compounds I and II. Stretching vibrations of the O—H and N—H bonds in compounds III and IV are manifested in the form of a broad, intense signal in the 3100-3500 cm^{-1} interval. Signals of the carbamoyl and thiocarbomoyl fragments of compounds I, III, and IV

TABLE 3. Chemical Shifts of Nuclei in ^{13}C NMR Spectra of Compounds I-VI

Compound	C=O (C—O)	NC=O (NC=S)	OCH_3 (SCH_3)	C—N	Signals of other carbon nuclei
Ia	208,9	156,3	51,2	46,8	42,8; 27,8; 13,8
Ib	205,1	154,8	51,3	51,3	50,7; 31,1; 27,3; 27,3
Ic	211,8	155,0	56,4	55,8	50,9; 43,6; 31,1; 30,2;28,9; 28,0; 25,4; 25,2; 21,0; 21,0
IIIb	(64,3)	155,5	50,6	51,8	49,5; 27,9; 25,2; 24,7
IVb	(64,2)	(195,3)	(17,5)	58,8	49,4; 26,4; 24,5; 22,6
Va cis	(75,5)	154,2	—	44,4	28,5; 15,8; 10,9
V a trans	(78,3)	154,5	—	45,3	31,6; 18,4; 13,5
Vb	(70,1)	154,5	—	49,8	41,5; 30,2; 28,9; 20,5
Vc cis	(71,4)	153,2	—	54,2	46,7; 38,3; 36,9; 35,0; 34,1; 32,3; 32,1; 30,1; 25,0; 24,9
and trans	(74,7)	154,3	—	54,4	24,6; 24,6; 24,3; 23,6; 21,6; 21,3; 20,2; 20,2; 19,9; 18,9
VIa trans	(80,6)	(186,1)	—	46,1	30,5; 18,0; 13,8
VIa cis	(77,7)	(185,80)	—	45,7	27,6; 15,8; 11,2
VIb	(73,5)	(186,4)	—	53,1	41,6; 30,3; 29,4; 21,1

appear at 1695-1710 and 1520-1530 cm^{-1}, respectively. In the IR spectra of 2% solutions of the 1,3-oxazin-2-ones V in chloroform, there is an intense band of absorption by the carbamoyl group in the 1710-1720 cm^{-1} region, and also signals of vibrations of the N—H bond in dimers of these compounds [14] at 3260-3270 cm^{-1}, and vibrations of the free N—H bond at 3440-3460 cm^{-1}.

By analysis of the NMR spectra, we established that reduction of the carbamate Ia and also reductive cyclization of compounds Ia,c and IIa lead to the formation of a mixture of erythro and threo isomers of IIIa and geometric isomers of tetrahydro-1,3-oxazines Va,c and VIa in equal ratios.

Thus, in our investigation of the behavior of N-(3-oxoalkyl)carbamates I and -dithiocarbamates II under conditions of borohydride reduction, we have shown that, depending on the pH of the medium, the reaction may lead either to the formation of N-(3-hydroxyalkyl) carbamates III and -dithiocarbamates IV, or to the formation of tetrahydro-1,3-oxazin-2-ones V and -oxazine-2-thiones VI. Considering the accessibility of the esters of N-(3-oxoalkyl)carbamic acids (which may be obtained, for example, by amidoalkylation of ketones and their derivatives [4], and also considering the simplicity of the reductive cyclization procedure, this method is of interest as a preparative route to tetrahydro-1,3-oxazin-2-ones. The pH−controlled borohydride reduction of 3-(oxoalkyl)carbamates and -dithiocarbamates may be used to obtain the corresponding hydroxy derivatives; this method competes successfully with other known methods [4, 15].

EXPERIMENTAL

^1H NMR spectra were recorded on a Bruker WM-250 spectrometer (250 MHz) and a Tesla BS-467 spectrometer (60 MHz) on 10-20% solutions in $CDCl_3$, with HMDS internal standard. ^{13}C NMR spectra were registered on a Bruker WP-80 spectrometer (20.13 MHz). IR spectra were registered on Specord IR-71 and UR-20 instruments, with the crystalline substances in the form of 2% solutions in $CHCl_3$ or suspensions in white mineral oil, and with the liquid specimens in a thin layer. Hydrochlorides of the 1,3-aminoketones were obtained by a procedure given in [16]; the methyl N-(3-oxoalkyl)dithiocarbamates IIa,b were obtained by a procedure given in [5].

Elemental analyses of the synthesized compounds for C, H, N, and S matched the calculated values.

Methyl N-(3-Oxoalkyl)carbamates (Ia-c). To 0.145 mole of the hydrochloride of the 1,3-aminoketone in 10.3 ml of water and 36.6 ml of ether, at −5° to −10°C with vigorous stirring, 0.145 mole of sodium hydroxide in 9 ml of water was added; then, 0.147 mole of methyl chloroformate and 0.147 mole of sodium hydroxide in 9 ml of water were added simultaneously from two dropping funnels. Then the cooling was discontinued, and the mixture was stirred at room temperature for 30 min; the precipitated sodium chloride was dissolved in 10 ml of water. The organic layer was separated,

and the aqueous layer was extracted with chloroform (3 × 25 ml). The combined extract was dried with magnesium sulfate, the solvent was driven off, and the residue was vacuum-distilled. Compound Ic was purified by sublimation.

Methyl N-(3-Hydroxyalkyl)carbamates (IIIa,b) and -Dithiocarbamates (IVa,b). To a suspension of 10.42 g of sodium dihydrogen phosphate, 23.82 g of sodium monohydrogen phosphate, and 22 mmoles of the ester Ib or IIb in 150 ml of methanol, 22 mmoles of sodium borohydride in 8 ml of water was added dropwise with stirring. After 1 h, 150 ml of water and 100 ml of ether were added to the reaction mass; the organic layer was separated, and the aqueous layer was extracted with ether (3 × 70 ml). The combined ether extract was washed with water (2 × 100 ml) and dried with magnesium sulfate, and the ether was driven off. Compounds Ia and IIa were reduced analogously without the addition of the buffer mixture. The carbamates IIIa,b were purified by vacuum distillation, the dithiocarbamates IVa,b by column chromatography on silica gel with 5:1 ether:chloroform eluent.

Tetrahydro-1,3-oxazin-2-ones (Va-c) and 2-thiones (VIa,b). To a solution of 24.5 mmoles of the ester Ia,c or IIa in 40 ml of alcohol, 24.5 mmoles of sodium borohydride was introduced in portions; the mixture was stirred for 1 h, after which 20 ml of a 5 M sodium hydroxide solution in alcohol was added, and the reaction mixture was allowed to stand overnight. Then the alcohol was driven off, and the residue was dissolved in 20 ml of water and extracted with chloroform (3 × 30 ml). The combined chloroform extract was washed with water and with a saturated solution of sodium chloride and then dried over calcium chloride, after which the solvent was driven off. Compounds Vb and VIb were obtained analogously from Ib and IIb without the addition of the sodium hydroxide solution.

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